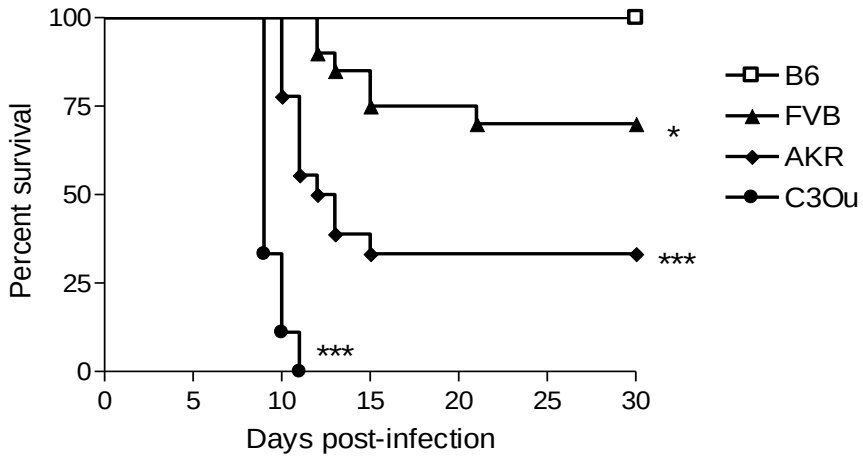
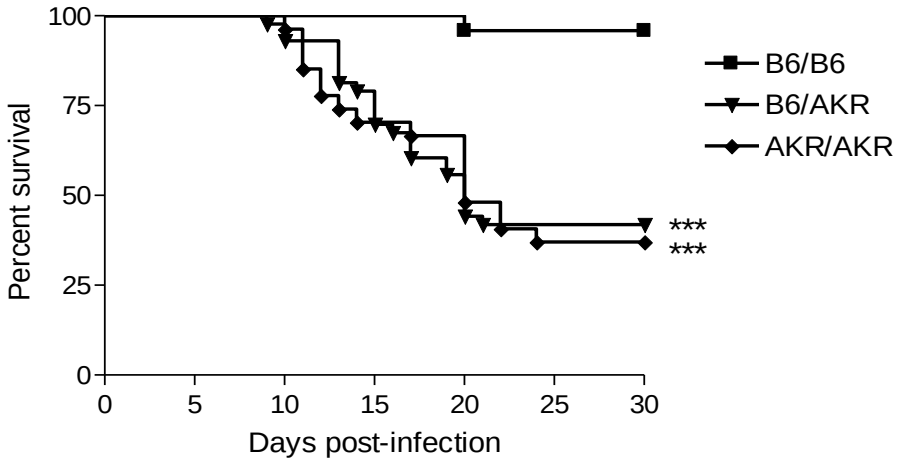
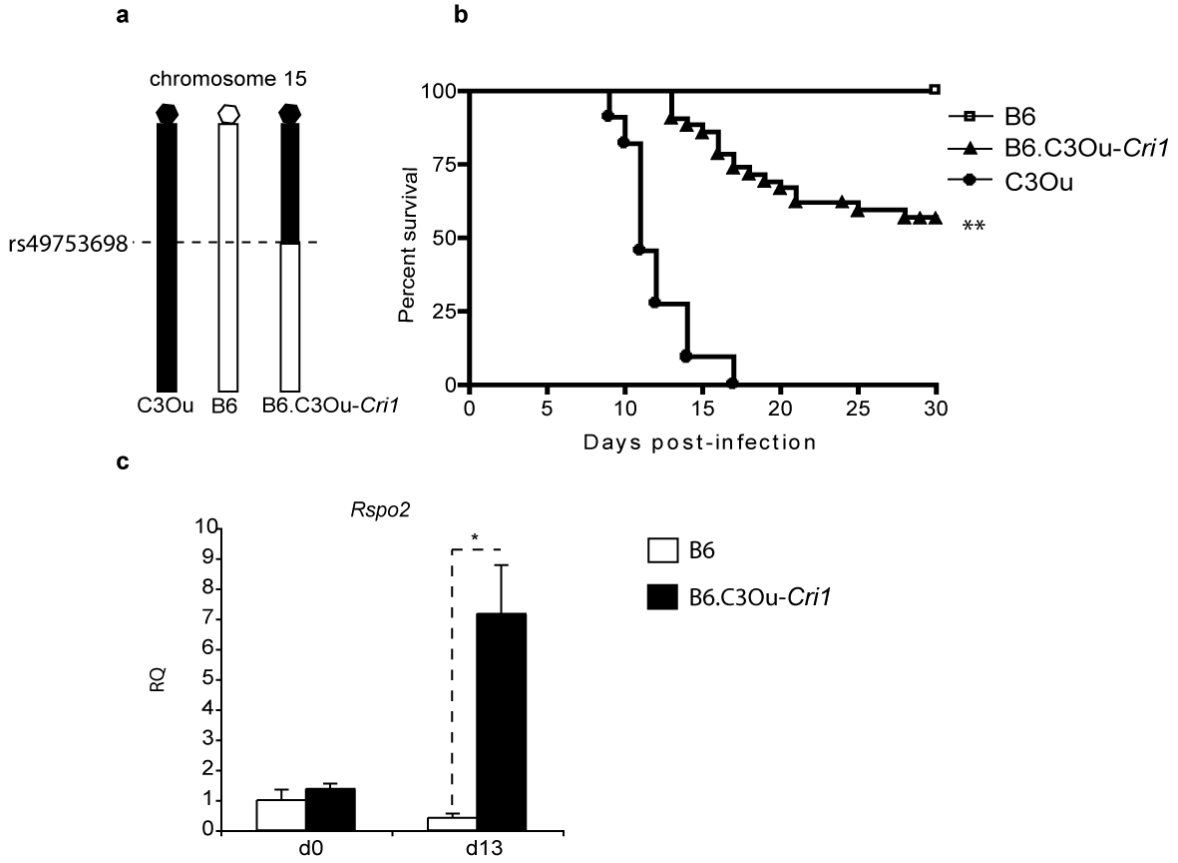


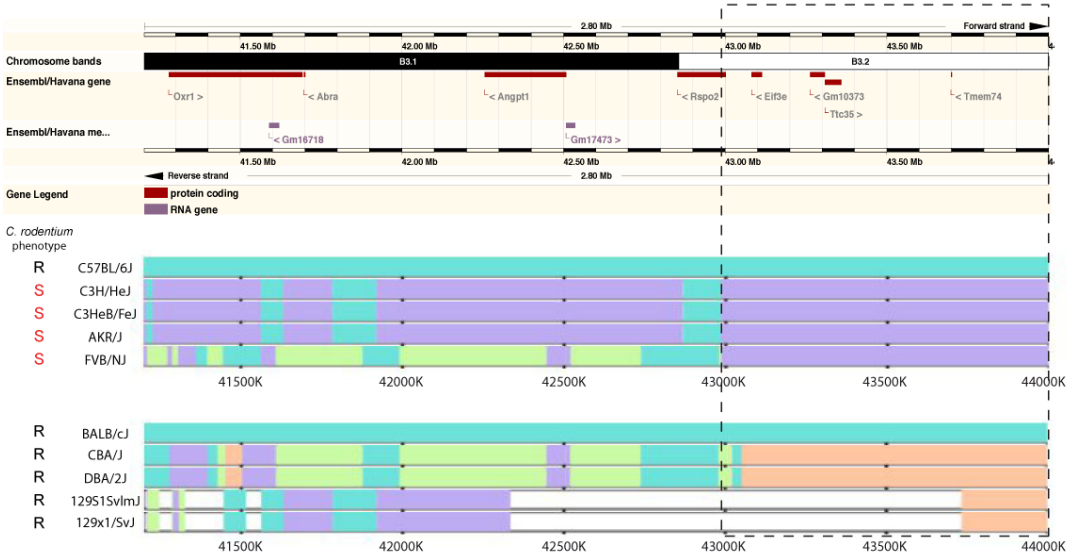
Supplementary Figure S1: Survival of inbred mice strains following infection with *Citrobacter rodentium*. Survival curves of C57BL/6 (B6, open squares, n=12) C3H/HeOuJ (C3Ou, filled circles, n=9), FVB/NJ (FVB, triangles, n=20) AKR/J mice (AKR, diamonds, n=18) following oral infection with *C. rodentium*. Results shown represent combined data from three infections. Statistical differences between survival curves were calculated using the logrank test. Survival curves of all susceptible strains are significantly different from B6; FVB *p=0.0413, AKR ***p=0.0004, C3Ou ***p<0.0001.



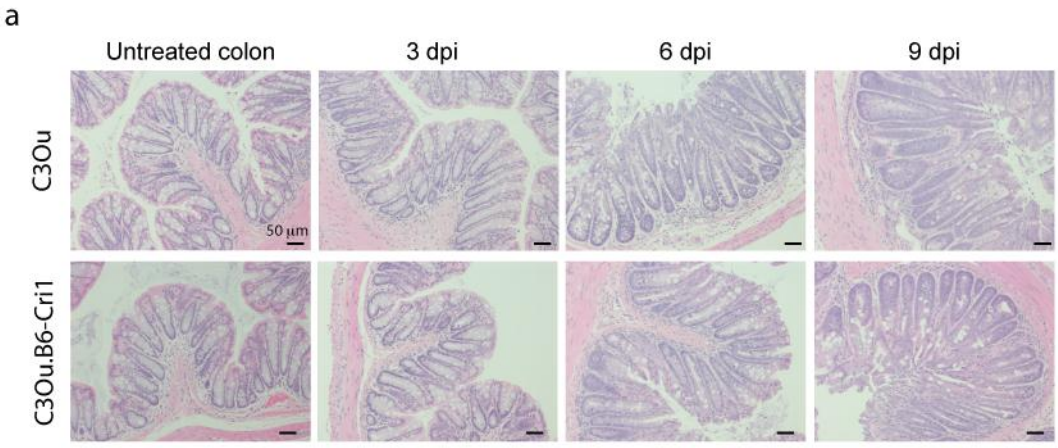
Supplementary Figure S2: *Cri1* controls *C. rodentium* susceptibility in AKR mice. (B6xAKR) F2 mice infected with *C. rodentium* and survival was monitored. Mice were genotyped at rs3683812, a SNP marker located at the peak of *Cri1*. Of the 94 F2 mice that were homozygous for the AKR allele at this marker (diamonds), 37% survived (n=27). Of the mice that were heterozygous at this marker (triangles), 42% survived (n=43). F2 mice that were homozygous B6 at *Cri1* (squares) had 96% survival at day 30 (n=24). Statistical differences between pairs of survival curves of mice grouped by genotype were calculated using logrank test. *** $p<0.0001$.



Supplementary Figure S3: *Cri1* controls susceptibility to *C. rodentium* infection in the resistant B6 genomic background. (**a**) Genetic map of chromosome 15 in C3Ou, B6 and B6.C3Ou-*Cri1* mice. Black indicates regions from C3Ou genome and white indicate regions from C3Ou genome. The congenic fragment of susceptible C3Ou genome in B6.C3Ou-*Cri1* mice extends from the telomere to marker rs49753698 (45.16 MB). (**b**) Survival of B6, C3Ou, congenic B6.C3Ou-*Cri1* mice following oral infection with *C. rodentium*. 45% of B6.C3Ou-*Cri1* mice succumb to infection between day 13 and day 28 post-infection. n=40, **p=0.0069. (**c**) Relative quantification (RQ) of *Rspo2* expression assayed by qPCR in whole colon tissues of resistant B6 and susceptible B6.C3Ou-*Cri1* mice left uninfected or 13 days after oral infection with *C. rodentium* (n=4).



Supplementary Figure S4: Haplotype map of *Cri1* candidate region. Data from the Mouse Phylogeny Viewer (http://msub.csbio.unc.edu/#viewer) indicating haplotype blocks in the *Cri1* candidate region as delineated by genetic and physical mapping. Strains analyzed were C57BL/6J mice (*Cri1*-resistant; R), *Cri1*-susceptible mouse strains (C3H/HeJ[13], C3HeB/FeJ (data not shown; also conserved in C3H/HeOuJ), FVB/J, AKR/J; S), and several other inbred mouse strains that are phenotypically resistant (R) to *C. rodentium* infection (ref. 10 and data not shown). *Cri1*-susceptibile mice share a common specific haplotype block that is not present in any of the resistant mouse strains (boxed) that extends from inside the second intron of *Rspo2* to the distal boundary of the prioritized interval.



Supplementary Figure S5: The Cri1 locus controls kinetics and magnitude of *C. rodentium* induced proliferation. (a) representative pictures of H&E stained FFPE sections of distal colon from C3Ou or C3Ou.B6-*Cri1* mice left untreated for the indicated time points after infection. Data are representative of three experiments. Quantification of crypt lengths is shown in Figure 4 of the manuscript.

Supplementary Table S1. Genetic Associations of *RSPO3* variants with Crohn's Disease (CD) in the IBDGC Meta-Analysis Summary Statistics.

rs#	Position	P_{meta} (CD)
rs719726	127456494	3.20E-05
rs719727	127456531	6.40E-05
rs2800708	127479310	4.30E-05
rs1936806	127493358	1.90E-05
rs1936805	127493809	2.80E-05
rs2489623	127497514	6.40E-06
rs2503322	127498953	5.10E-06
rs1936802	127503375	5.10E-06
rs9491699	127505338	5.20E-05
rs3734626	127513226	1.10E-05
rs1892172	127513484	3.70E-05
rs2489629	127518209	2.60E-05
rs4644087	127518410	3.70E-05
rs2489631	127532292	2.60E-05
rs6569474	127535304	3.40E-05
rs7745274	127550850	4.90E-05
rs10457487	127560927	3.20E-05

Note: Odd's Ratio for the CD meta-analysis were not reported in the summary statistics. Positions correspond to chromosome 6.

Supplementary Table S2. Genetic Associations of *RSPO3* Variants with Ulcerative Colitis (UC) in the IBDGC Meta-Analysis Summary Statistics.

rs#	Position	P_{meta} (UC)	OR (95% C.I.)
rs2745342	127468799	6.51e-05	1.85(1.36-2.51)
rs2745337	127474869	5.55e-05	1.86(1.37-2.52)
rs2800706	127475484	8.96e-05	1.76(1.30-2.37)

Note: Positions correspond to chromosome 6.

GWAS data analysis. Recent Inflammatory Bowel Genetics Consortium (IBDGC; http://medicine.yale.edu/intmed/ibdgc/index.aspx) Crohn's disease [20] and ulcerative colitis [19] meta-analyses were scanned for significantly associated SNPs in the genes RSPO1-4. SNPs with $P<10^{-4}$ were included in the analysis. Significant variants, in addition to SNPs found to be in linkage disequilibrium (L.D.) using SNAP (SNP Annotation and Proxy Search; http://www.broadinstitute.org/mpg/snap/), were analyzed with pfSNP for potential function (pfs.nus.edu.sg/).

Supplementary Methods

SNP	Position	Forward Primer	Reverse Primer
RS3698904	5052173	TTACCAAGGTGCCTTAAGCTG	TCTGCAGTGGGCTTGAGAC
RS3714893	20812230	CAGACAATCACAGTTATCCTTGG	CCTTTTGGCACTGTGAAAGA
RS3704632	41203245	CACTTTTGTCACTGGATTGCT	CATTCACAGTCATACATCATGT
RS3681536	41630333	CAAGCGATCGTATTAAACATCT	TGTGGTAGACTTCATTCCATG
RS33305068	44029444	TCCAGGAAGCAGGTAAGCAG	TGCCATCAGCTAAGTAGGGC
RS49753698	45164270	TCATGCCACACACACCAAG	TTTGTCTATTTGTGACAATCTC
RS33336560	46058799	AAATCAATTGGGATTTTCTTTG	TGGAGAAAAGGGGAATTAGTC
RS3719583	48898332	GGCTAAGCTGTTGGAACTTCTC	GAAGTTGTCTTCTTAGTTGAAAG
RS3702158	56992041	GGATACTGAGAAAGGCCCAG	ATCCCTTCGAGGCAAGTACA
RS3656705	62640499	AATGAGCGAATGACTGAGCC	CATAGTCTTCTCCCTGTCTGG

	Forward Primers	Reverse primers
c-Myc	TGACCTAACTCGAGGAGGAGCTGGAATC	AAGTTTGAGGCAGTTAAAATTATGGCTGAAGC
Mmp7	GCATTTCCTTGAGGTTGTCC	CACATCAGTGGGAACAGGC
Klf4	GAAGGTCGTGGCCCCGGAAAAG	ATCGGAGCGGGCGAATTTCCAC
Clca3	CCAACTGAACAACAACGGC	GCCTGAGTCACCATGTCCTT
Slc26a3	ACAAAAGTCTGTCCTGGCAGCGC	TGCCGCCAGGCCTAATCCGA
Car4	GCATGATCGCGACGCCTAGGG	CCACTTCTCAGGCCCCAAGCAA
Hprt	GTTGGATACAGGCCAGACTTTGTTG	GATTCAACTTGCGCTCATCTTAGGC

Recombinant DKK1. The DKK1 cDNA was amplified from cDNA purchased from TrueClone (SKU# MC201891) using the primers Forward: gaattcatgatggttgtgtgtgcagcg gcagctgtccg and Reverse: gctccacacctgccagagacaccatcatcaccatcaccatcac cat gga gga cag tga gcggccgc. The reverse primers add an 8 residue his tag to the protein. The DKK1 coding region was cloned using TOPO vector system (Invitrogen) and from TOPO was subcloned into the pTT5 vector [1, 2]) at the EcoR1 and Not1 sites. DKK1 protein was produced in

suspension-growing 293-6E cells by large-scale (2L) transfection as previously described [3] with some modifications. 293-6E cells were grown and transfected in F17 medium (Gibco) supplemented with 0.1% (w/v) Kolliphor (Sigma) at a density of 1,5 to 2,0x10^6 cells/mL using PEIpro (Polyplus[4]) at a plasmid DNA:PEI ratio of 1:1 (w/w). Six hours post-transfection, heparin (Sigma) and tryptone N1 (TN1, Organotechnie) were added at 0.1g/L and 0.5% (w/w) respectively. Five days post-transfection, culture medium was harvested, 220 mL of 10 X concentrated buffer A (200 mM imidazole, 500 mM Tris, 1 M NaCl, pH 8.0) was added and the medium clarified by filtration through a 0.45 µm membrane. The DKK1 protein was then purified by immobilized metal affinity chromatography using a 10 mL Fractogel-chelate column pre-charged with cobalt as previously described [5]. Purity of the protein was estimated to be >95% as analyzed by SDS-PAGE and Coomassie staining.

Supplementary References

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